

PATENT

Appl. No. 10/694,641  
Amdt. dated June 13, 2006  
Reply to Office Action of December 29, 2005

Amendments to the Claims:

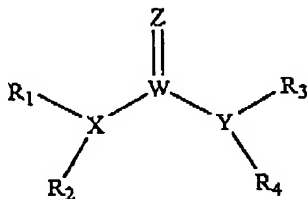
This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claims 1-13 (Canceled)

14. (Currently amended) A method of reducing blood pressure in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase ("sEH"), which inhibitor inhibits by 50% the epoxide hydrolyzing activity of sEH at a concentration of less than about 500  $\mu$ M.

15. (Previously presented) A method of claim 14, wherein the inhibitor is a compound having a structure of:



wherein Z is oxygen or sulfur, W is carbon phosphorous or sulfur, X and Y is each independently nitrogen, oxygen, or sulfur, and X can further be carbon, at least one of R<sub>1</sub> - R<sub>4</sub> is hydrogen, R<sub>2</sub> is hydrogen when X is nitrogen but is not present when X is sulfur or oxygen, R<sub>4</sub> is hydrogen when Y is nitrogen but is not present when Y is sulfur or oxygen, R<sub>1</sub> and R<sub>3</sub> is each independently C<sub>1</sub> -C<sub>20</sub> substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, or heterocyclic.

Appl. No. 10/694,641

PATENT

Amdt. dated June 13, 2006

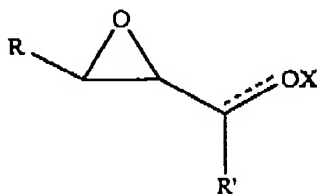
Reply to Office Action of December 29, 2005

16. (Previously presented) A method of claim 15, wherein W is carbon and Z is oxygen.

17. (Previously presented) A method of claim 15, wherein X is nitrogen.

18. (Previously presented) A method of claim 15, wherein Y is nitrogen.

19. (Withdrawn) A method of claim 14, wherein the inhibitor is a compound having a structure of:



wherein R is alkyl or aryl, the compound is *trans*-across the epoxide ring, OX is a carbonyl (O) or hydroxy group (OH), and R' is a H, alkyl or aryl group.

20. (Withdrawn-currently amended) A method of claim 19, wherein said inhibitor has a structure wherein R, R', and X--Y are as follows:

(a) when R is C<sub>6</sub>H<sub>5</sub>, R' is C<sub>6</sub>H<sub>5</sub>, and X--Y is selected from the group consisting of: C=O, CH-OH, C=NOH, S=O, and CH-OCH<sub>3</sub>,

(b) when R is 4-F-C<sub>6</sub>H<sub>4</sub>, R' is C<sub>6</sub>H<sub>5</sub>, and X-Y is selected from the group consisting of C=O and CH-OH;

(c) when R is 4-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is C<sub>6</sub>H<sub>5</sub>, X-Y is selected from the group consisting of C=O, CH-OH, C=NOH, S=O and CH-OCH<sub>3</sub>;

(d) when R is 4-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, X-Y is selected from the group consisting of C=O and CH-OH;

PATENT

Appl. No. 10/694,641

Amtd. dated June 13, 2006

Reply to Office Action of December 29, 2005

(e) when R is  $C_{10}H_7$ , R' is  $C_6H_5$  and X-Y is C=O;

(f) when R is 4- $NO_2-C_6H_4$ , and R' is  $CH_3$ , X-Y is selected from the group consisting of C=O and CH-OH; or

(g) when R is 4- $NO_2-C_6H_4$ , and R' is H, X-Y is CH-OH.

21. (Previously presented) A method of claim 14, wherein the inhibitor is a pharmaceutically acceptable salt.

22. (Previously presented) A method of claim 14, wherein the inhibitor is administered orally.

23. (Previously presented) A method of claim 14, wherein the inhibitor is administered in a total daily dose from about 0.001  $\mu M/kg$  to about 100 mg/kg body weight of the patient.

24. (Canceled.)

25. (Canceled)

26. (Previously presented) A method of claim 14, wherein said blood pressure reduction comprises a reduction in systolic blood pressure.

27. (Previously presented) A method of claim 14, wherein said patient has high normal blood pressure.

28. (Previously presented) A method of claim 14, wherein the patient is at risk for cardiovascular disease, renal disease, or stroke.

PATENT

Appl. No. 10/694,641

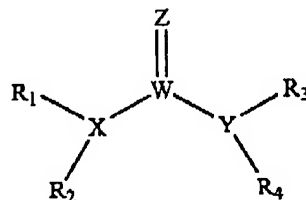
Amdt. dated June 13, 2006

Reply to Office Action of December 29, 2005

29. (Previously presented) A method of claim 14, wherein the patient has cardiovascular disease or renal disease.

30. (Currently amended) A method of reducing hypertension in a patient, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase ("sEH"), which inhibitor inhibits by 50% the activity of sEH in hydrolyzing epoxides at a concentration of less than about 500  $\mu$ M.

31. (Previously presented) A method of claim 30, wherein the inhibitor is a compound having a structure of:



wherein Z is oxygen or sulfur, W is carbon phosphorous or sulfur, X and Y is each independently nitrogen, oxygen, or sulfur, and X can further be carbon, at least one of R<sub>1</sub> - R<sub>4</sub> is hydrogen, R<sub>2</sub> is hydrogen when X is nitrogen but is not present when X is sulfur or oxygen, R<sub>4</sub> is hydrogen when Y is nitrogen but is not present when Y is sulfur or oxygen, R<sub>1</sub> and R<sub>3</sub> is each independently C<sub>1</sub> -C<sub>20</sub> substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, or heterocyclic.

32. (Previously presented) A method of claim 31, wherein W is carbon and Z is oxygen.

33. (Previously presented) A method of claim 31, wherein X is nitrogen.

Appl. No. 10/694,641

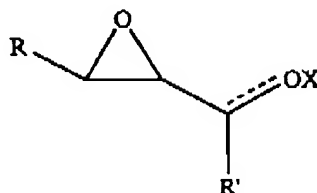
Amdt. dated June 13, 2006

Reply to Office Action of December 29, 2005

PATENT

34. (Previously presented) A method of claim 31, wherein Y is nitrogen.

35. (Withdrawn) A method of claim 30, wherein the inhibitor is a compound having a structure of:



wherein R is alkyl or aryl, the compound is *trans*-across the epoxide ring, OX is a carbonyl (C=O) or hydroxy group (OH), and R' is a H, alkyl or aryl group.

36. (Withdrawn-currently amended) A method of claim 35, wherein said inhibitor has a structure wherein R, R', and X--Y are as follows:

(a) when R is C<sub>6</sub>H<sub>5</sub>, R' is C<sub>6</sub>H<sub>5</sub>, and X--Y is selected from the group consisting of: C=O, CH--OH, C=NOH, S=O, and CH--OCH<sub>3</sub>,

(b) when R is 4-F-C<sub>6</sub>H<sub>4</sub>, R' is C<sub>6</sub>H<sub>5</sub>, and X--Y is selected from the group consisting of C=O and CH--OH;

(c) when R is 4-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is C<sub>6</sub>H<sub>5</sub>, [[X-y]] X-Y is selected from the group consisting of C=O, CH--OH, C=NOH, S=O and CH--OCH<sub>3</sub> ;

(d) when R is 4-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, X-Y is selected from the group consisting of C=O and CH--OH;

(e) when R is C<sub>10</sub>H<sub>7</sub>, R' is C<sub>6</sub>H<sub>5</sub> and X-Y is C=O;

(f) when R is 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is CH<sub>3</sub>, X-Y is selected from the group consisting of C=O and CH--OH; or

(g) when R is 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>, and R' is H, X-Y is CH--OH.

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PATENT

37. (Previously presented) A method of claim 30, wherein the inhibitor is a pharmaceutically acceptable salt.

38. (Previously presented) A method of claim 30, wherein the inhibitor is administered orally.

39. (Previously presented) A method of claim 30, wherein the inhibitor is administered in a total daily dose from about 0.001 M/kg to about 100 mg/kg body weight of the patient.

40. (Previously presented) A method of claim 30, wherein the hypertension is essential hypertension.

41. (Previously presented) A method of claim 30, wherein said reduction of hypertension comprises reducing systolic blood pressure.

42. (New) A method of claim 14, wherein said inhibitor totally inhibits the epoxide hydrolyzing activity of sEH at a concentration of 100  $\mu$ M.

43. (New) A method of claim 30, wherein said inhibitor totally inhibits the epoxide hydrolyzing activity of sEH at a concentration of 100  $\mu$ M.

44. (New) A method of claim 42, wherein the inhibitor is administered in a total daily dose from about 0.001  $\mu$ M/kg to about 100 mg/kg body weight of the patient.

45. (New) A method of claim 43, wherein the inhibitor is administered in a total daily dose from about 0.001  $\mu$ M/kg to about 100 mg/kg body weight of the patient.